20. (Amended) A method of delivering a heterologous gene to an animal heart *in vivo*, wherein the method comprises administering to the animal heart an adenoviral vector comprising (a) a heterologous gene; (b) a promoter positioned upstream from the heterologous gene, the heterologous gene being under the regulatory control of the promoter; (c) a eukaryotic splice acceptor and donor site positioned downstream of the promoter and upstream of the heterologous gene; and (d) a polyadenylation sequence.

REMARKS

Examiner Interview

Applicant wishes to thank Examiner Schnizer for the courtesy extended to Applicant's agent, Heather R. Kissling, in the telephone interview conducted on April 18, 2001. The Saito et al. and French et al. references were discussed in the course of the telephone interview. Applicant is most appreciative of the Examiner's time.

The Present Invention

The present invention is directed to an adenoviral vector for expressing a heterologous gene(s) in a host cell, a host cell infected with such a vector, a method of producing a selected protein by culturing a host cell infected with such a vector, and a method of delivering a heterologous gene to an animal heart *in vivo* by administering such a vector to the animal heart.

Amendments to the Claims

Claims 1, 3, and 20 have been amended to point out more particularly and claim more distinctly the present invention. In particular, claims 1 and 3 have been amended to recite a heterologous promoter. Claim 20 has been amended to recite a promoter. The amendments to the claims are supported by the specification at, for example, page 9, lines 3-9, page 16, lines 26-35, and page 18, lines 11-25. No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the claims, as well as the text of the pending claims as amended, are attached hereto.

The Pending Claims

Claims 1, 3, 4, 9, and 17-20 are currently pending. Claims 1, 3, 4, 9, and 17 are directed to the adenoviral vector, whereas claim 18 is directed to the host cell, claim 19 is directed to the method of producing a selected protein, and claim

20 is directed to a method of administering a heterologous gene to an animal heart *in vivo*.

The Office Action

Claims 1 and 9 are rejected under 35 U.S.C. § 101, for allegedly being directed to non-statutory subject matter. Claims 1 and 9 further are rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Cladaras et al., *Virology*, *140*(1), 44-45 (1985) (abstract provided). Claims 1, 9, and 17-19 are rejected under 35 U.S.C. § 102(e), as allegedly being anticipated by U.S. Patent 5,731,172 (Saito et al.). Claims 1, 3, 4, 9, and 17-20 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious in view of Kirshenbaum et al., *J. Clin. Invest.*, *92*, 381-389 (1993); Quantin et al., *Proc. Natl. Acad. Sci. USA*, *89*, 2581-2584 (1992); or Stratford-Perricaudet et al., *J. Clin. Invest.*, *90*, 626-630 (1992); in view of Huang et al., *Nucl. Acid Res.*, *18*(4), 937-347 (1990); Choi et al., *Mol. Cell. Biol.*, *11*(6), 3070-3074 (1991); Keating et al., *Exp. Hematol.*, *18*, 99-102 (1990); WO 91/00747 (KabiGen et al.); and U.S. Patent 5,731,172 (Saito et al.) (claims 1, 3, 4, 9, and 17-19) and further in view of Kitsis et al., *PNAS*, *88*, 4138-4142 (1991) or French et al., *Circulation*, 90(5), 2414-2424 (1994) (abstract provided) (claim 20). Reconsideration of these rejections is hereby requested.

Discussion of Rejection under Section 101

The Office has rejected claims 1 and 9 as allegedly being drawn to non-statutory subject matter. In particular, the Office contends that the subject matter of claims 1 and 9 encompass naturally occurring adenovirus, and cites Cladaras et al. in support of its contention. Claim 1, as amended, is directed to an adenoviral vector comprising a heterologous promoter. As such, claims 1 and 9 cannot be considered to encompass naturally occurring adenovirus, and the rejection should be withdrawn.

Discussion of Rejection under Section 102(b)

The Office has rejected claims 1 and 9 under Section 102(b), as allegedly being anticipated by Cladaras et al. Claim 1, as amended, is directed to an adenoviral vector comprising a heterologous promoter. Cladaras et al. does not teach or suggest incorporating a heterologous promoter into an adenoviral vector. Thus, Cladaras et al. does not teach each and every aspect of claims 1 and 9. In view of the amendment to claim 1, the rejection under Section 102(b) is moot.

Discussion of Rejection under Section 102(e)

The Office has rejected claims 1, 9, and 17-19 under Section 102(e), as allegedly being anticipated by U.S. Patent 5,731,172 (Saito et al.). As pointed out to the Examiner in the telephonic interview of April 18, 2001, the instant application is a continuation of a parent application that was filed on December 14, 1993, which predates the filing date of Saito et al. (September 8, 1994). Thus, Saito et al. is not available as prior art under Section 102(e). Accordingly, the rejection of claims 1, 9, and 17-19 under Section 102(e) should be withdrawn.

Discussion of Rejection under Section 103(a)

The Office has rejected claims 1, 3, 4, 9, 17, 18, and 19 as allegedly being obvious in view of and, therefore, unpatentable over Kirshenbaum et al., Quantin et al., or Stratford-Perricaudet et al., in view of Huang et al., Choi et al., Keating et al., WO 91/00747 (Kabigen et al.), and U.S. Patent 5,731,172 (Saito et al.). Claim 20 has been rejected as allegedly being obvious over the cited references and further in view of Kitsis et al. and French et al. This rejection is traversed for the reasons set forth below.

In the Office Action of August 23, 1999, the Office rejected the pending claims of the instant application in view of Kirshenbaum et al., Quantin et al., or Stratford-Perricaudet et al., in view of Huang et al., Choi et al., Keating et al., and WO 91/00747 (Kabigen et al.). The Office further contended that one of ordinary skill in the art would have been motivated to combine the disclosures of the primary and secondary references because of the disclosed value of the disclosed components to increase gene expression in other contexts (i.e., other gene transfer vectors) and because each genetic component would have been expected to function in the same manner in an adenoviral vector.

As set forth in Applicant's Amendment of May 30, 2000, Quantin et al., Kirshenbaum et al., and Stratford-Perricaudet et al. do not teach or suggest the use of a splice acceptor and donor site located between a promoter sequence and a heterologous gene to be expressed in an adenoviral vector. The secondary references cited by the Office, e.g., Huang et al., Choi et al., Keating et al., and KabiGen et al., none of which are directed to adenoviral vectors, do not cure the deficiencies of Quantin et al., Kirshenbaum et al., and Stratford-Perricaudet et al. (see Amendment of May 30, 2000, at, for example, page 6, first paragraph).

In combining the cited references, the Office alleged that the ordinarily skilled artisan would have expected the disclosed genetic elements, described in the context of non-adenoviral constructs, to function similarly in an adenoviral vector. On the contrary, one of ordinary skill in the art would not have combined

the references as alleged by the Office with a reasonable expectation of, for example, successfully increasing gene expression by insertion of a heterologous splice site into adenovirus, as evidenced by the Declaration under 37 C.F.R. § 1.132, executed by Dr. Imre Kovesdi and submitted May 30, 2000. According to Dr. Kovesdi, regulatory sequences can have different activity in adenovirus than in other expression systems. Indeed, the ordinarily skilled artisan would not have expected a heterologous splice site to increase gene expression in an adenoviral vector as alleged by the Office (see Rule 132 Declaration, paragraphs 9-11).

Applicant's arguments were deemed unpersuasive by the Office in view of Saito et al., and the Office maintained that the ordinarily skilled artisan would have been motivated to combine the references cited above with a reasonable expectation of success (see Office Action of March 6, 2001, page 7, paragraph 3). However, as set forth above, Saito et al. is not prior art to the instant application and, thus, cannot be properly cited in a Section 103(a) rejection. The Office has not provided any reasonable scientific argument or cited any relevant literature (aside from possibly Saito et al.) that contradicts the content of the Rule 132 Declaration of Dr. Kovesdi. The Office has provided no reasonable evidence supporting its position that the ordinarily skilled artisan would have expected the genetic elements of the cited references to function in adenovirus and, therefore, has not established a *prima facia* case of obviousness. Moreover, the Office has not provided any reasonable evidence that an ordinarily skilled artisan would have expected the genetic elements of the cited references to function in adenovirus with the results attendant the present invention. Under the circumstances, the subject matter of claims 1, 3, 4, 9, 17, 18, and 19 cannot be considered obvious in view of the cited references.

With respect to claim 20, the Office contends it would have been obvious to deliver the vector of Kirshenbaum et al., Quantin et al., Stratford-Perricaudet et al., Huang et al., Choi et al., Keating et al., Kabigen et al., and Saito et al. to an animal heart in view of the teaching of French et al. and Kitsis et al. Contrary to the assertion of the Office, the administration of the present inventive vector to an animal heart to deliver a heterologous gene to the animal heart would not have been obvious to the ordinarily skilled artisan in view of the cited references at the time of filing of the instant application. First, the claimed adenoviral vector is not obvious over Kirshenbaum et al., Quantin et al., Stratford-Perricaudet et al., Huang et al., Choi et al., Keating et al., Kabigen et al., and Saito et al. for the reasons set forth above. Second, Applicant notes that French et al. was available to the public as of November, 1994, which is after the filing date of the instant application. As such, French et al. is not prior art to the instant application,

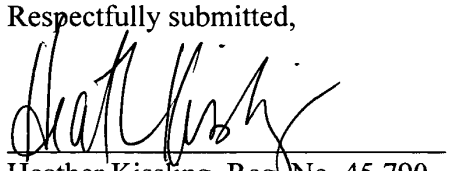
leaving only Kitsis et al. to be relied upon by the Office as allegedly teaching the delivery of an adenoviral vector to an animal heart. Third, there is no teaching or suggestion in Kitsis et al. to administer an adenoviral vector to an animal. Kitsis et al. is merely directed to the injection of naked DNA into heart or skeletal muscle, not injection of adenoviral vectors. Moreover, it is not clear that the plasmids described in Kitsis et al. even comprise the genetic elements of the presently claimed adenoviral vectors, e.g., a eukaryotic splice acceptor and splice donor site. In that Kitsis et al. does not teach or suggest injection of adenoviral vectors, or any vector comprising the genetic elements of the presently claimed adenoviral vector, into an animal heart, one of ordinary skill in the art simply would not have been motivated to combine Kitsis et al. with the other references cited by the Office to arrive at the present invention. Thus, the subject matter of claim 20 cannot be considered obvious in view of the cited references.

In view of the above, Applicant submits that the subject matter of claims 1, 3, 4, 9 and 17-20 cannot be considered obvious over the cited references. Accordingly, Applicant requests withdrawal of the rejection under Section 103(a).

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

By: 

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Date: June 4, 2001

CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: June 4, 2001 Frances Sanchez

PATENT
Attorney Docket No. 201895

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Falck-Pedersen

Application No. 08/653,114

Filed: May 24, 1996

For: ADENOVIRUS GENE EXPRESSION SYSTEM

Group Art Unit: 1632

Examiner: R. Schnizer

AMENDMENTS TO CLAIMS ON JUNE 4, 2001

1. (Twice Amended) An adenoviral vector for expressing a heterologous gene(s) in a host cell, comprising (a) at least one insertion site for cloning a selected heterologous gene; (b) a heterologous promoter [sequence] positioned upstream from said at least one insertion site, wherein, upon cloning of the selected heterologous gene into said at least one insertion site, said gene is under the regulatory control of said heterologous promoter; (c) a eukaryotic splice acceptor and splice donor site positioned downstream of said promoter and upstream of said at least one insertion site; and (d) a polyadenylation sequence positioned downstream of said insertion site.

3. (Twice Amended) The adenoviral vector according to Claim 1, wherein said heterologous promoter [sequence] is a mouse cytomegalovirus early promoter, or an effective expression promoting fragment thereof.

20. (Amended) A method of delivering a heterologous gene to an animal heart *in vivo*, wherein the method comprises administering to the animal heart an adenoviral vector comprising (a) a heterologous gene; (b) a promoter [sequence] positioned upstream from the heterologous gene, the heterologous gene being under the regulatory control of the promoter; (c) a eukaryotic splice acceptor and donor site positioned downstream of the promoter and upstream of the heterologous gene; and (d) a polyadenylation sequence.